REMARKS

Introductory Comments

Claims 1-7, 9-19, 21 and 22 are pending. The Office has rejected all pending claims.

The Office has rejected claims 1-4, 9, 11, 12, 14-19, 21 and 22 under 35 U.S.C. §102(a), alleging that the claims are anticipated by U.S. Patent No. 5,900,238 to Gombotz *et al.*

The Office has rejected claims 1-7, 9-19, 21 and 22 under 35 U.S.C. §103(a), alleging that the claims were obvious over U.S. Patent No. 5,900,238, in view of Partidos *et al.* (1996) Immunology, and EP 0517565 to Callegaro *et al.*

Applicants acknowledge with appreciation the withdrawal of the previous rejections under 35 U.S.C. §101 and 35 U.S.C. §112, second paragraph. The remaining rejections are traversed and believed to be overcome for reasons discussed below.

Overview of the Amendments

Claim 1 has been amended to recite that the composition also comprises a detoxified mutant of a bacterial ADP-ribosylating toxin selected from the group consisting of LT-K63 and LT-R72. The amendment finds support in the claims as originally filed, and page 23, line 8 to page 24, line 12 of the application.

Claims 1 and 11 have been amended to recite that the antigen is not entrapped in the microsphere. The amendment finds support on page 12, line 15 to page 13, line 2, and page 28, line 1 to page 31, line 10.

Claim 1 has been amended to correct for dependency.

No new matter has been added by way of these amendments.

1. The Rejection of Claims 1-4, 9, 11, 12, 14-19, 21, and 22 under 35 U.S.C. §102(a)

The Examiner has maintained the rejection of claims 1-4, 9, 11, 12, 14-19, 21 and 22 under 35 U.S.C. §102(a), alleging that the claims are anticipated by U.S. Patent No. 5,900,238 to Gombotz *et al.*

Gombotz *et al.* disclose antigens encapsulated in a stabilized hydrogel microbead (abstract). Gombotz *et al.* further state that their invention provides a composition where an antigen is encapsulated in a hydrogel microbead (column 2, lines 38-40).

In order to anticipate, a single source must contain all of the elements of the claim. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379, 231 USPQ 81, 90 (Fed. Cir. 1986). The recitations of previous claim 5, not subject to the rejection, have been added to claim 1. Gombotz *et al.* does not disclose a detoxified mutant of a bacterial ADP-ribosylating toxin as now recited in independent claim 1. In addition, the reference does not disclose an hyaluronic acid ester polymer selected from the group consisting of an hyaluronic acid where from about 75% to about 100% of free carboxyl groups are esterified with one or more alkyl groups, and a crosslinked derivative of hyaluronic acid in which about 0.5% to about 20% of the carboxyl groups of the hyaluronic acid polymer are crosslinked to hydroxyl groups of the same or a different hyaluronic acid molecule as recited in independent claim 11. Since Gombotz *et al.* does not disclose all the elements of the independent claims, the applicants invention is not anticipated. Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §102(a).

In the Official Action, the Examiner stated that the applicants' arguments submitted on March 27, 2002, citing several legal precedent in support of their position, were "in direct conflict with the directions of the MPEP" §2131.02 (page 3). The applicants disagree with the statement that their arguments conflicted with the MPEP. The last paragraph of MPEP §2131.02 states:

> Compare In re Meyer, 599 F.2d 1026, 202 USPQ 175 (CCPA 1979) (A reference disclosing "alkaline chlorine or bromine solution" embraces a large number of species and cannot be said to anticipate claims to "alkali metal hypochlorite."); Akzo N.V. v. International Trade Comm'n, 808 F.2d 1471, 1 USPQ2d 1241 (Fed. Cir. 1986) (Claims to a process for making aramid fibers using a 98% solution of sulfuric acid were not anticipated by a reference which disclosed using sulfuric acid solution but which did not disclose using a 98% concentrated sulfuric acid solution.). See MPEP §§ 2144.08 for a discussion of obviousness in genus-species situations.

The applicants had cited the holding of *Akzo* in support of their position. The MPEP section does not direct an examiner to automatically reject a claim as anticipated where a genus-species situation might exist. Instead, the MPEP directs the examiner to consider the facts of each case in light of the prior art disclosure.

In addition, the foreword to the MPEP states that the purpose of the manual is to provide guidance and specifically states that the manual does not have the force of law. Morever, the federal circuit in *Molins PLC v. Textron, Inc.*, 48 F3d 1172, 1180 n.10 (1985) noted that the MPEP was not binding on the court but was entitled to judicial notice as an official interpretation of statutes or regulations as long as it was not in conflict. Thus, if MPEP is in conflict with case law cited by the applicants in support of their position, then case law applies. Case law makes clear that where a reference does not highlight a claimed mixture among the many dozen disclosed or suggested, the reference is not sufficient to anticipate claims reciting the specific combination. In the present case, Gombotz *et al.* does not specifically call out or suggest applicants' particular combinations from the laundry list of possible polymers that could be used to make hydrogels, therefore it cannot anticipate the applicants' claims.

Regardless, Gombotz *et al.* does not disclose a detoxified mutant of a bacterial ADP-ribosylating toxin or a crosslinked derivative of hyaluronic acid in which about 0.5% to about 20% of the carboxyl groups of the hyaluronic acid polymer are crosslinked to hydroxyl groups of the same or a different hyaluronic acid molecule. Therefore, the claims are not anticipated.

2. The Rejection of Claims 1-7, 9-19, 21 and 22 under 35 U.S.C. §103(a)

The Examiner has maintained the rejection of claims 1-7, 9-19, 21, and 22 under 35 U.S.C. §103(a), alleging that the claims were obvious over U.S. Patent No. 5,900,238, in view of Partidos *et al.* (1996) Immunology, and EP 0517565 to Callegaro *et al.* The Examiner states that Gombotz *et al.* do not disclose claimed adjuvants or using influenza, but Partidos *et al.* teach LT-K63 as an effective mucosal adjuvant, and Callegaro *et al.* teach the use of hydaluronic ester microspheres for intranasal application of a protein.

The applicants traverse the rejection. In order to render claims obvious, the burden is on the Office to establish a *prima facie* case of obviousness for which three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations. The teachings or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Applicants submit that the cited references do not provide a a motivation to modify the cited references. Thus, a *prima facie* case of obviousness has not been presented by the Office.

The applicants reiterate Gombotz *et al.* disclose a laundry list of additional hydrogels that could be used to form a microsphere, and is not enabling for a composition comprising an hyaluronic acid ester polymer in the form of a microsphere and a selected antigen. Therefore, the Office has not presented a *prima facie* case of obviousness. In addition, due to the failure of the reference to provide an enabling disclosure, the combination of references do not provide a reasonable expectation of success, and the rejection should be withdrawn.

However, in order to further prosecution, the applicants have amended the independent claims 1 and 11 such that the antigens are not encapsulated in the microspheres. The antigens of Gombotz *et al.* are encapsulated in agilate microbeads. The results in Table 1 of Gombotz *et al.* (column 12, lines 1-13) show only that antibodies encapsulated in poly-L-lysine coated beads elicit an antibody response. An antibody titer of 10,000 was observed when OVA-specific-IgG antibody in coated beads were administered, but titers of 50 and less than 50 were observed for the administration of a mixture containing the antigen and empty coated beads, and empty coated beads alone, respectively. At column 12, lines 30-32, the reference states: "Only OVA encapsulated and released from poly-L-lysine coated beads showed an OVA IgG antibody titer of 10,000."

The applicants' claims pertain to compositions where the antigen in not entrapped in the microspheres. In contrast, the results of Gombotz *et al.* require that the antigen be encapsulated in the coated beads. Further, Gombotz *et al.* presents experimental data showing antigen that was not encapsulated in the coated beads did not elicit an immune response. Thus, there would be no motivation to combine the teachings of Gombotz *et al.* with the disclosure of Partidos *et al.* and Callegaro *et al.* to arrive at the applicants' compositions, and there would be no expectation of success The Office is respectfully requested to withdraw this rejection.

Improper rejection

The applicants reiterate that the rejection of claims 1-4, 9, 11, 12, 14-19, 21 and 22 as anticipated by Gombotz *et al.*, and a separate rejection of the same claims as obvious over Gombotz *et al.*, in view of Partidos *et al.* and Callegaro *et al.* is improper. If the primary reference was thought to contain all the elements of the applicants' invention as defined by the above claims, and therefore anticipatory, then combination with secondary references to provide missing elements to make those claims obvious would be unnecessary.

CONCLUSION

Applicants respectfully submit that the claims comply with the requirements of 35 U.S.C. §§101, and 112 and define an invention that is patentable over the art. Accordingly, a Notice of Allowance is believed in order and is respectfully requested.

Please send all further written communications in this case to:

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APPENDIX A

Marked up Version of The Claims.

Claims 4, 9, 10, 12 and 13 were canceled.

Claims 1, 5 and 11 were amended as follows:

1. (Amended) A composition comprising an hyaluronic acid ester polymer in the form of a microsphere, a detoxified mutant of a bacterial ADP-ribosylating toxin, and a selected antigen, wherein said antigen is present in an amount of approximately .1% to about 40% (w/w) antigen to hyaluronic acid polymer, and wherein said antigen is not entrapped in the microsphere.

5. The composition of claim [4] 1, wherein the [adjuvant is a] detoxified mutant of a bacterial ADP-ribosylating toxin selected from the group consisting of LT-K63 and LT-R72.

11. (Amended) A composition comprising (a) a microsphere comprised of an hyaluronic acid ester polymer selected from the group consisting of an hyaluronic acid where from about 75% to about 100% of free carboxyl groups are esterified with one or more alkyl groups, and a crosslinked derivative of hyaluronic acid in which about 0.5% to about 20% of the carboxyl groups of the hyaluronic acid polymer are crosslinked to hydroxyl groups of the same or a different hyaluronic acid molecule; (b) a selected antigen [entrapped in, or] adsorbed to[,] the microsphere, wherein said antigen is present in an amount of approximately 2% to about 25% (w/w) antigen to hyaluronic acid polymer; and (c) an immunological adjuvant.

APPENDIX B

Clean Copy of Claims Pending

1. (Twice Amended) A composition comprising an hyaluronic acid ester polymer in the form of a microsphere, a detoxified mutant of a bacterial ADP-ribosylating toxin, and a selected antigen, wherein said antigen is present in an amount of approximately .1% to about 40% (w/w) antigen to hyaluronic acid polymer, and wherein the antigen is not entrapped in the microsphere.

2. The composition of claim 1, wherein said antigen is present in an amount of approximately 2% to about 25% (w/w) antigen to hyaluronic acid polymer.

3. The composition of claim 1, wherein the hyaluronic acid ester is selected from the group consisting of an hyaluronic acid where from about 75% to about 100% of free carboxyl groups are esterified with one or more alkyl groups, and a crosslinked derivative of hyaluronic acid in which about 0.5% to about 20% of the carboxyl groups of the hyaluronic acid polymer are crosslinked to hydroxyl groups of the same or a different hyaluronic acid molecule.

5. The composition of claim 1, wherein the detoxified mutant of a bacterial ADP-ribosylating toxin selected from the group consisting of LT-K63 and LT-R72.

6. The composition of claim 1, wherein the selected antigen is a viral antigen.

7. The composition of claim 6, wherein the selected antigen is an influenza antigen.

11. (Amended) A composition comprising (a) a microsphere comprised of an hyaluronic acid ester polymer selected from the group consisting of an hyaluronic acid where from about 75% to about 100% of free carboxyl groups are esterified with one or

more alkyl groups, and a crosslinked derivative of hyaluronic acid in which about 0.5% to about 20% of the carboxyl groups of the hyaluronic acid polymer are crosslinked to hydroxyl groups of the same or a different hyaluronic acid molecule; (b) a selected antigen adsorbed to the microsphere, wherein said antigen is present in an amount of approximately 2% to about 25% (w/w) antigen to hyaluronic acid polymer; and (c) an immunological adjuvant.

14. A method of making a pharmaceutical composition which comprises combining the composition of claim 1 with a pharmaceutically acceptable mucosal excipient.

15. A method of making a pharmaceutical composition which comprises combining the composition of claim 11 with a pharmaceutically acceptable mucosal excipient.

16. A method of immunization which comprises mucosally administering a therapeutically effective amount of the pharmaceutical composition of claim 14 to a vertebrate subject.

17. A method of immunization which comprises mucosally administering a therapeutically effective amount of the pharmaceutical composition of claim 15 to a vertebrate subject.

18. The method of claim 16 wherein the administering is done intranasally.

19. The method of claim 17 wherein the administering is done intranasally.

21. The composition of claim 1, wherein the microsphere is a nanosphere.

22. The composition of claim 11, wherein the microshphere is a nanosphere.